

WEBVTT

NOTE duration:"00:37:54.6000000"

NOTE language:en-us

NOTE Confidence: 0.919687211513519

00:00:00.020 --> 00:00:23.510 Aaron ring and I'm delighted to introduce our next set of speakers. Our first speaker, especially for this particular symposium needs no introduction from delighted to do it anyway. And that's my colleague doctor leaping chin, who's the United Technologies Corporation Professor in Cancer Research and professor of Immunobiology Dermatology in Madison.

NOTE Confidence: 0.667385220527649

00:00:24.060 --> 00:00:26.150 So leaping please.

NOTE Confidence: 0.645780444145203

00:00:27.230 --> 00:00:30.160 Tell us what you.

NOTE Confidence: 0.503159284591675

00:00:33.970 --> 00:00:37.710 See very soon.

NOTE Confidence: 0.881887018680573

00:00:50.720 --> 00:00:56.370 OK thanks for the for the invitation.

NOTE Confidence: 0.866680085659027

00:00:57.530 --> 00:01:00.480 I have uh so today this disclosure my.

NOTE Confidence: 0.740167319774628

00:01:01.910 --> 00:01:03.460 So the

NOTE Confidence: 0.882705926895142

00:01:04.230 --> 00:01:15.830 Today, actually this is my talk will be break 2. Two Part 1 is first I will tell you briefly what we learn from these anti PD one PD L1 study which?

NOTE Confidence: 0.877784788608551

00:01:16.660 --> 00:01:33.730 We have have been going on in my lab for more than 20 years. So we urge you to learn quite a bit of stuff I will briefly summarize what we learn and what's the key is key point we learn and then I will show you use this principle we learn?

NOTE Confidence: 0.872786283493042

00:01:34.470 --> 00:01:42.170 Use that as a foundation and then to learn and to further progress and tie by that principle and into.

NOTE Confidence: 0.856857180595398

00:01:42.680 --> 00:02:12.850 Develop the new therapies you therapy means this could be a next generation and could be a better better. One so the case for immunology. Traditionally, you view. This case immunology as the kind of car racing game that you have cancer growing in the body and you have immunity try to play catch up so immunity developed. Obviously, based on this morning. There were lots of lots of lectures. I think is a basic.

NOTE Confidence: 0.876576662063599

00:02:12.850 --> 00:02:19.840 Principle we understand is the one tumor growing there's a lot of things available to you for immune system too.

NOTE Confidence: 0.809913277626038

00:02:20.450 --> 00:02:25.240 To be to be stimulated and cancel the release of energies and.

NOTE Confidence: 0.888737559318542

00:02:25.990 --> 00:02:40.260 Trigger the immune response so the so this is a kind of traditional view. So then the based on that would be if the immunity can capture more powerful than the immunity name because.

NOTE Confidence: 0.865979850292206

00:02:40.790 --> 00:02:45.190 Other way around in many cases, particularly in the tumor patient.

NOTE Confidence: 0.879780828952789

00:02:45.850 --> 00:03:03.660 Well, we, we see what we see is the case of beat immunity is because immunity is not really pretty culture, so in this traditional view. Then this why I've mentioned that is because based on this then totally different idea to develop different type of email service.

NOTE Confidence: 0.840141177177429

00:03:04.210 --> 00:03:34.730 So currently current view based on more basic immunology study, then we know there's not a simply these 2 is 2. Things out of raising raising the body is more like cancer actually be immunity also by developed immune evasion mechanism. This evasion mechanism. It should prevent very KIRO to shutdown immunity. You write a different way. So then in this case, the immunity never catch up.

NOTE Confidence: 0.858717024326324

00:03:34.730 --> 00:03:51.950 OK, so the based on this 2 different view and in a lot of evidence of the research. Then the my mind is cancelled in new serapi can be clearly divided to 2 different type and based on 2 different ideas.

NOTE Confidence: 0.88937121629715

00:03:52.450 --> 00:04:00.570 First type, which is being a very traditional as being used for many, many years, probably more than 50 years now code enhancement.

NOTE Confidence: 0.854595899581909

00:04:01.230 --> 00:04:14.960 I just summarizing hasten anyways. Where is based on the idea is a mission is the you have a two cars racing in the body and then intrinsic community is not sufficient and that meaning they're not cannot picture.

NOTE Confidence: 0.869577884674072

00:04:15.470 --> 00:04:16.310 So then.

NOTE Confidence: 0.888782918453217

00:04:17.390 --> 00:04:47.450 The approach there will be just two promoting stronger immunity to generate better immunity to enhance the normal immune response. So then you basically promoting all entire process of the immune response just to raise the immune response and now we actually doing pretty well in the field of the cancer immunology. You can use particular way. Cytokines vaccines, or write different way and then you can enhance normal immunity, too much higher level.

NOTE Confidence: 0.768906474113464

00:04:47.450 --> 00:04:49.230 Then normal level.

NOTE Confidence: 0.870733141899109

00:04:49.880 --> 00:05:03.700 Now isolated adapter transfer of Diesels. For example, you can raise immunity 200 times or even 1000 times, then the normal physiological level. So it's so it's already the colors are cheap.

NOTE Confidence: 0.865799129009247

00:05:04.390 --> 00:05:34.560 Then the but based on the another idea, which is the immune response is often defect. It's because of racial mechanism developer cancer, then idea then is to repair the defective immune response rather than just promoting in general to raise the immune response. You specifically go. Find out what is wrong, there and then to correct that defect so this actually call.

NOTE Confidence: 0.923521995544434

00:05:34.560 --> 00:05:35.990 Normalization approach.

NOTE Confidence: 0.86251837015152

00:05:36.700 --> 00:05:54.290 So you can see this is very different. The way to look the immunity so this cartoons and show the differences of these 2 types of approaches the on the Top or is this a weakened escriba. Simi response as the water flows through the pipe.

NOTE Confidence: 0.878546476364136

00:05:54.810 --> 00:06:15.610 Normally water just go through it cause it would rain and if tumor start growing which indicated here by there's a block in the middle of the type. Then there's a different way to do. One is to really increase the pressure increase the water pressure for example, to push through the.

NOTE Confidence: 0.701642751693726

00:06:16.370 --> 00:06:18.470 The water so too.

NOTE Confidence: 0.769691169261932

00:06:19.190 --> 00:06:20.110 Hopefully, 2.

NOTE Confidence: 0.780532479286194

00:06:20.720 --> 00:06:22.240 To pursue this block.

NOTE Confidence: 0.904331922531128

00:06:22.900 --> 00:06:35.660 So that is enhancement approaches and normalization would be to identify what's the problem and where is it and then selectively move that particular block so you can see this is a quite different?

NOTE Confidence: 0.889350473880768

00:06:36.540 --> 00:06:46.300 So this slide basically summarize what we learn from many years, many, many years of study on the.

NOTE Confidence: 0.855944097042084

00:06:46.990 --> 00:07:17.320 P1 and P DL1 as you many of you know, and this morning also loud speakers. His talk about. We know the anti. PD one APT L1 is very unique therapy therapy in a couple of ways. One is there's a very broad spectrum. They can cover very lots of indications in case which means it efficient. It's effective in many different table cases, which different from the enhancement approaches.

NOTE Confidence: 0.909040749073029

00:07:17.320 --> 00:07:20.470 Which is usually limited to a particular type of cancers?

NOTE Confidence: 0.842646300792694

00:07:21.020 --> 00:07:51.530 With so-called more image any tumors and also the toxicity is much lower compared with enhancement so the differently, something quite different need to Relearn. So we summarize as the three essential the principles. One is the type of therapy has to identify what type of invasion mechanism is these type of evasion mechanism is associated with tumor progression.

NOTE Confidence: 0.864990234375

00:07:51.660 --> 00:08:00.240 Meaning is in normal tissue such mechanism mechanism is not present or minimally present.

NOTE Confidence: 0.881117165088654

00:08:00.840 --> 00:08:23.440 So this is a zodia with skins or what they will induce by case, number, 2 is immune evasion mechanism appears to be frequently happened in the tumor microenvironment, meaning in the tumor site. Very few of those mechanisms develop systemically so that again is very different from enhancement enhancement as I mentioned to you.

NOTE Confidence: 0.860306799411774

00:08:24.340 --> 00:08:41.420 Often is the novel generation of the new immune response so usually get systemic boost of the emirate's bars #3 is the target master switch, which is reprogram or reset your response I think this is getting very critical now.

NOTE Confidence: 0.903741896152496

00:08:42.210 --> 00:08:51.300 For this particular issue is the as we know also you can see, there's a lot of data presented in this morning in the if you analyze the?

NOTE Confidence: 0.873772025108337

00:08:52.080 --> 00:09:22.090 The nearest bars in the tumor. Michael environment, you can see, there's a multiple mechanism can be Co present in the UG for example, say you have P. DL1 always press. But you also have a teacher beta. You have teams relax really whatever whatever there's a series of of those, and the How do you know you just simply manipulate one single password and you can overcome immune response it seems impossible?

NOTE Confidence: 0.834121823310852

00:09:22.130 --> 00:09:30.510 Because there's a multiple possibly it's all if all operating then you just manipulating one how you get you can reverse.

NOTE Confidence: 0.863458752632141

00:09:31.010 --> 00:09:48.150 The suppression immune response seems impossible right so the key. However, this argument has been going on actually for more than 30 years, OK, even with before we started work. We started to isolated the molecule are like a PDA or one that argue is already there, OK, I can tell you the.

NOTE Confidence: 0.865273594856262

00:09:48.760 --> 00:09:59.500 The in that time, we don't believe it. We don't believe is multi mechanism can act simultaneously.

NOTE Confidence: 0.867078542709351

00:10:00.120 --> 00:10:30.270 The way right now looks like it is there's maybe multiple mechanism available, but always one will take a dominant seat OK. If this storm didn't see fail. Then there's another one click in very few we see very few cases will occasionally you could see you might see in the patient. Then you can see maybe both mechanisms are very strong, the inhibit immune response, but many cases is single dominant mechanism payroll.

NOTE Confidence: 0.861243367195129

00:10:30.300 --> 00:10:35.930 The opportunity OK, you can manipulate you single pass away, you can actually read up lots of cancers.

NOTE Confidence: 0.883686900138855

00:10:36.580 --> 00:10:43.320 So this is important is to identify what to target particular mask must switch so then the.

NOTE Confidence: 0.881541609764099

00:10:43.870 --> 00:11:00.180 There's a little confusing concept in the field call also called email checkpoint OK OK. I can tell you this is quite confusing. The concept and is very different from what this normalization. We talk about first any checkpoint is.

NOTE Confidence: 0.86281806230545

00:11:01.410 --> 00:11:34.520 Can be any normal immune inhibitory mechanism typically is like for example, CTR 4 city 04 is required for the control of the auto immune autoimmunity autoimmunity, so reactivities, you get rid of the mouse. You knockout knockout molecules. You don't even have to give them any enerji my style already so it's required physiologically so this is one part of normal, inhibitory mechanism, which require for keep the peace of the response.

NOTE Confidence: 0.895848095417023

00:11:34.680 --> 00:11:42.190 So it is a very different. We talk about this is tumor induced a mechanism, so this is not part of a normal the control.

NOTE Confidence: 0.942295849323273

00:11:42.860 --> 00:11:44.020 #2 is

NOTE Confidence: 0.881386995315552

00:11:44.690 --> 00:11:46.560 The checkpoint can be.

NOTE Confidence: 0.852719306945801

00:11:47.640 --> 00:12:09.520 Most of the Mitchell is boosting sustainability that we talk about this. The normalization is frequently happen in the tool. UG and he also checkpoint is not really target master switch. This is there's no evidence so far showing that so also based on this concept so calling me checkpoint, the many, many different target being.

NOTE Confidence: 0.718941509723663

00:12:10.170 --> 00:12:12.460 Put in the criminal there, too.

NOTE Confidence: 0.858008921146393

00:12:13.260 --> 00:12:40.350 To test the efficacies these are all single agent, I listed and this every single agent fell in the clinical trial. A single agent. This is just a chore is a short list. There's a more more than that it should probably double that so the I think we have enough the evidence. I think showing is not just simply checkpoint will work is not just any has to be very selective.

NOTE Confidence: 0.911286056041718

00:12:42.770 --> 00:12:44.430 So how we approach it then.

NOTE Confidence: 0.839637994766235

00:12:45.090 --> 00:12:47.560 How we approach this question is the?

NOTE Confidence: 0.819640636444092

00:12:48.230 --> 00:13:01.640 As a summation early the PD one PD L1. It works in fraction notation, but we know is works about quarter patient late stage cancer about 25%.

NOTE Confidence: 0.89207124710083

00:13:02.190 --> 00:13:10.180 So there's a lot of other case, the patient. What is what happened happened in the immune response to those measures?

NOTE Confidence: 0.884736061096191

00:13:10.910 --> 00:13:22.300 So this is the we, we try to approach this question OK. This is one of the very simple classification of human cancer. These all advanced human solid tumors.

NOTE Confidence: 0.852381765842438

00:13:22.800 --> 00:13:38.110 And we start with them in an oma and then later goes to all the different type of cases and I'm going to show you in a minute, so this is this is the classification. This is these are time time classification? Is is the tumor immunity in the micro environment.

NOTE Confidence: 0.854519248008728

00:13:38.940 --> 00:13:47.990 And you can see on the left is the P. TL1 or a piece of expression. OK, based on that and then the array in the bottom is the.

NOTE Confidence: 0.7917240858078

00:13:48.530 --> 00:13:55.430 It is Weasel is Artie sauce, so you can see this is clearly there's on Top are left.

NOTE Confidence: 0.842089772224426

00:13:56.010 --> 00:14:27.980 The couple level or or lower right. This is more single positive and in the lower part which is the label is type one which is double negative on the right upper upper corner is the double positive, which is do have posed he sells and the P. DL1 expression so by this way. Then you can see this very different profile. Clearly, there's a hero. GDP of the human case is quite different. It's just based on this very simple 22 parameters, you already can see this.

NOTE Confidence: 0.87365996837616

00:14:27.980 --> 00:14:57.820 Quite that most so this is a summary of the variety different. The study from first from us. There's a few study for us and then there's a lot of others or pulled together from different type of cancer showing left when a normal. This is your how many cases 256. This is our only study published 2012 and then there's a long cancer. Prater columns or these different type of cases and you can see the first type is double negative which means there's no.

NOTE Confidence: 0.85158234834671

00:14:58.360 --> 00:15:06.740 Piso infiltration OK and then obviously there's an opium. One also so that's double negative which is basically is.

NOTE Confidence: 0.833534121513367

00:15:07.250 --> 00:15:37.530 It's there's no immune response in the UG so typically this double negative type of cases immunologist is walk away. They say well. There's no email response so that's not my business. But if his case an immunologist. Then you have to take it so that's a different differences of immunologist versus cancer immunology so second type is double positive, which as I mentioned this type, which is the best as your response to.

NOTE Confidence: 0.765950500965118

00:15:37.530 --> 00:15:38.790 Or benefit best.

NOTE Confidence: 0.819208025932312

00:15:39.300 --> 00:15:40.410 From the

NOTE Confidence: 0.826152265071869

00:15:41.050 --> 00:15:46.160 PD1PD at Alliance Arripis, there, which is about quarter quarter of the of the patient.

NOTE Confidence: 0.868961811065674

00:15:47.230 --> 00:15:59.580 And it I'm sorry is have a teaser infiltration, but there's no P. DL1 OK, so these pretty obvious. This is teaser still dysfunctional is immediate by some other mechanism then.

NOTE Confidence: 0.843504786491394



00:16:00.240 --> 00:16:12.780 Then the PP want people don't want that because pedia ones, not even there so there must be something else. So the Type 4 is the P DL1 positive that there's.

NOTE Confidence: 0.854038178920746

00:16:13.450 --> 00:16:27.410 But there's no real teaser infiltration like this is often due to the genetic mutation, which directly hit the password. RP DL1, so people. One is expressed automatically is not even needed to be induced.

NOTE Confidence: 0.853615522384644

00:16:28.100 --> 00:16:58.790 And as we know pedia one is typically induced by interval Gamma, released by the link for Scio and K cells in a tumor UG right. But it's Type 4 don't fit. This is a genetic mutations, which theoretically ternal so, based on this you can see this is we see in the middle type of tool corner, which is about 2520 four 25%, which is about quarter of can benefit from these therapies and I was 3 is the healthy cells. But other mechanism right so this is a.

NOTE Confidence: 0.895838558673859

00:16:58.820 --> 00:17:02.030 Population we actually very interested so let me show you some.

NOTE Confidence: 0.847938001155853

00:17:02.670 --> 00:17:28.100 Some data today and how we based on this. The classification with develop our next generation self. So this type 2 as I mentioned this is larger than my benefit from a seller. Please type of story is non PD one. PD L1 mechanism. Obviously type one and 4, which is today. We still working on that and I'm not going to talk about today. Hopefully soon in the future.

NOTE Confidence: 0.868396520614624

00:17:28.740 --> 00:17:31.610 So Type 2 as I mentioned the problem is.

NOTE Confidence: 0.888737261295319

00:17:32.440 --> 00:17:36.650 Diesel is clearly clearly infiltrating they recognize something like that.

NOTE Confidence: 0.859626829624176

00:17:37.170 --> 00:18:06.330 But the PD into one is not expressed so this must be something else. So we have actually developed the quite a many years ago. About 10 years ago, where you develop try to address this question. And we've developed a couple system, literally to address this so 12 platform, basically right now is running. One is called Receptor, A, which is developed by a very talent poster showing y'all.

NOTE Confidence: 0.867811679840088

00:18:06.880 --> 00:18:12.740 Share this in that time was control app and then he strained trained biochemist.

NOTE Confidence: 0.886943340301514

00:18:15.000 --> 00:18:32.980 OK, Mister for Mount Sinai and then as from from Albert Einstein, sorry and then in that time, we talk about developer system, which basically including as much as we can all the membrane proteins in our system so basically is we try to display.

NOTE Confidence: 0.849696218967438

00:18:33.530 --> 00:18:51.280 All possible membrane protein honor cell surface by that way, then if we want to identify the binding partner OK. They say this is reset the like an interaction so with this system, they have the very sensitive system to detect the protein interaction.

NOTE Confidence: 0.866166889667511

00:18:51.970 --> 00:19:24.010 This actually is not it's actually it is a big deal because we know in the in the field of the receptor likely interaction majority or cell membrane protein interaction are very low affinity? How low the best of cell membrane natural protein reset. The Liger Interaction, the best actually is probably 1, two to lower the lower than the worst. Monaco anybody meeting is worse tomorrow. Anybody the Infinity is still one or 2 log better than the best.

NOTE Confidence: 0.879822969436646

00:19:24.010 --> 00:19:33.790 Our cell surface protein interaction so with that issue. Then you can see this majority of receptor lie again identification work is very difficult.

NOTE Confidence: 0.851263523101807

00:19:34.460 --> 00:20:00.090 Right now actually is in probably 2 hours to re reset the light can be identified every year so that kind of slow speed. So we developed the first for the purpose, then #2, is when we have the system going we can. Display the molecule in the cell surface. This is thousands of jeans so that individually display in the cell service of the we choose to Nicely Cho cells.

NOTE Confidence: 0.849752426147461

00:20:00.640 --> 00:20:20.630 Then we develop is functional, functional array, OK, so basically wanted to know who wanted to develop a high throughput system, which you can edit. Display this protein and then very quickly identify? What kind of function. They have so this is one is the poster fellow and graduate student change way.

NOTE Confidence: 0.867991209030151

00:20:21.550 --> 00:20:35.660 Actually develop this system is the we have this label as 6500 membrane protein individually transfer into artificial entity imprisoning cells. These cells already have OK T sorry everybody.

NOTE Confidence: 0.832935988903046

00:20:36.310 --> 00:20:43.110 Expresses a membrane form, which means they can stimulate his US right, they can buy some cities, Rhiannon stimulate his ass.

NOTE Confidence: 0.851349055767059

00:20:43.690 --> 00:20:48.710 So then use that to mimic a teaser receptor signal, then this additional.

NOTE Confidence: 0.831346035003662

00:20:49.210 --> 00:21:14.340 Membrane protein expression well, then star Marjorie that ease of activity right. So so that's the idea. So modulation means either promoting or inhibited right. So then we do have a Reporter readout, which is in this case is another copy to show the TCR signal eventually can travel down down through the Passway and to have a sensitive reader or teaser, either get activated or inhibited.

NOTE Confidence: 0.840489387512207

00:21:14.960 --> 00:21:46.090 So by this way, this is one of one of display of the table, 100 jeans, a couple 100. The cell membrane protein activities in the middle of Mark Mark means is this is only cells with PCR signals so in the middle, then use that as the background. Then whatever things whatever the molecule can trigger above the mock is considered stima. Tori and lower than that, then consider is the.

NOTE Confidence: 0.855916023254395

00:21:46.090 --> 00:21:55.450 Inhibitors so that you can see this There's a variety differently mirrors, which is already being reported stimulators so the idea then is.

NOTE Confidence: 0.938599467277527

00:21:56.080 --> 00:21:57.220 We will have

NOTE Confidence: 0.86825704574585

00:21:58.060 --> 00:22:19.960 Will have these 2 platforms and screen. Wholesale jeans usually thousands of teen now. Even the thousands of jeans. The looks the quite a lot of work, but now we already automated system and now remember the entire human genome. There's only about 9000 teens so we're very close to.

NOTE Confidence: 0.853231430053711

00:22:20.820 --> 00:22:31.470 Will be able to run entire cell service member improving to detect to detect activities. So the idea is then with this Greening we will get a set up.

NOTE Confidence: 0.836315155029297

00:22:32.000 --> 00:23:02.190 The molecule which either inhibit immune response or stimuli response so let's focus on inhibitors if come over auntie so ATP array than if they inhibit immune response. Obviously this is one of the essay with multiple different ways, depending on what kind of question you're asking this kind of essay you can set up for alcovy readout. TCR signal you can set up for other things like probably for Asian or settle kind release, you can say whatever you want.

NOTE Confidence: 0.860741376876831

00:23:02.580 --> 00:23:18.730 So by that way, then we come out whole setup for Inhibitors, then we took that data and then to match what we found in the consultation OK. This is for example, as I mentioned a type III patience this type of sorry patience.

NOTE Confidence: 0.839844286441803

00:23:19.590 --> 00:23:37.780 Time is revision have we don't know what's there right there must be hypothesis is they must have some powerful inhibitors, there and the shutdown in response, and this powerful vehicular is not the PD one. PD L1 because they're not there, so then the.

NOTE Confidence: 0.868449687957764

00:23:38.330 --> 00:24:01.340 We will go through that data and then to a microarray or protein analysis and showing in a Type 3 patients. What kind of molecule overexpressed there and use that to match what we find out in our array so by that bench, then we pick the target this target is which is.

NOTE Confidence: 0.851645469665527

00:24:02.340 --> 00:24:32.350 Show activities in Alpha screening and then also showed right location, which is in a micro environment. Obviously, the express in minimal level in a normal tissue OK. This is as I mentioned that one hour. Criterias now goes to the numbers 3 criteria, which is this has to be a master switch. This has to be dominant. The emitters so we move to our visual in vivo logical essays to identify this molecule is.

NOTE Confidence: 0.867079019546509

00:24:32.470 --> 00:24:38.060 A dominant or not there in bright different system this system, including mouse models and they also.

NOTE Confidence: 0.848218083381653

00:24:38.570 --> 00:24:52.010 Lots of human studies that we also conduct so the one today. I'm going to show you one quickly. Show you one or molecules. We identified and this is now is already moved to clinic is called secret 15.

NOTE Confidence: 0.825066030025482

00:24:52.870 --> 00:25:23.360 As I mentioned this molecule is not come out by say teen family is a secret family or particular interest is not. This is the

Camera screen screening cannot screening it can be any genius that can be anything. Family can be can be something on now so this is a member of sialic acid binding. The electing family molecules is a large pieces, IG IG Vid Si Domain and then there's Indiana end of terminal this side.

NOTE Confidence: 0.732976317405701

00:25:23.360 --> 00:25:29.100 Yes, it binding motifs, which means they could interact with Sally acid.

NOTE Confidence: 0.826270282268524

00:25:29.940 --> 00:25:42.410 So now this is a type one protein OK and Y intercept domain. There's I think domain OK, so potentially this molecule could deliver single through the cell to be receptive actually.

NOTE Confidence: 0.812541306018829

00:25:43.460 --> 00:26:01.370 Normally this molecule are expressed in low level in my garage. My alloy sell some of my lawyer so useful field injury cells and pieces. The piece of osteoclast also expressed but it's very low level in general, very low level, even make cells.

NOTE Confidence: 0.950449347496033

00:26:01.910 --> 00:26:04.000 It's about 1520% of.

NOTE Confidence: 0.863106250762939

00:26:04.750 --> 00:26:31.330 Cells normally expressed this molecule in low level, so it's it is very low but in the case is much higher expression so this match. One of our criteria so this is the only data showing normal tissue is very minimal level on Top of the human data and there's a positive control is Mako veg in the mouse. You can see this very low level also in most issues.

NOTE Confidence: 0.804127156734467

00:26:32.580 --> 00:27:04.230 Now there in human cancer is clearly upper regulation. You can see this variety different type of cancers place RNA data. This is you can see predicates. Colon rectal skinny long. They all have a fraction of the patient could have a clearly operating Messenger RNA or signific team and this is David rain in the pathology department's work and you can see this is one example of many study, he had done is the long small cell lung cancer is.

NOTE Confidence: 0.863617777824402

00:27:04.230 --> 00:27:17.280 In the 159 cases, we see this 49 of them positive. You know based on these quantity email for license. The interesting Lee is the expression in the human cancer patient.

NOTE Confidence: 0.821678817272186

00:27:17.780 --> 00:27:31.920 Appears to be in either in the stroma because this is the cost remark, which is a red show is red, which is most likely the Mayo

sauce and then also in a tumor mask, which means this molecule are linked directly operated.

NOTE Confidence: 0.817180454730988

00:27:32.440 --> 00:27:54.220 On a cancer cell surface, so why then, we know most of these long small cell lung cancer. Cells are epithelial cells. So why or how this in theory, so can express this monitor which is quite surprised and buy anyway. This is this is the data the fact.

NOTE Confidence: 0.871721088886261

00:27:54.760 --> 00:28:09.610 And the another interesting thing is these signal 15 appears to be reversed inversely correlate with PPL why expression so that makes sense because we purposely looking at, I'm sorry monocus.

NOTE Confidence: 0.839352428913116

00:28:10.130 --> 00:28:22.210 The molecule in the type III cancer, which supposedly pedia. One is very low anyway, so which is actually match what we were hypothesis. So you can see this expression on the on the.

NOTE Confidence: 0.720941543579102

00:28:22.920 --> 00:28:24.340 Secret routine on.

NOTE Confidence: 0.837509632110596

00:28:24.870 --> 00:28:33.020 On on the Y axis the pedia one on on X axis. You can see this correlation is very, very weak, you have.

NOTE Confidence: 0.78663033246994

00:28:33.660 --> 00:28:39.110 Puppy Ste, 4 cases coordinated in couple 100 samples.

NOTE Confidence: 0.819837987422943

00:28:40.430 --> 00:29:10.500 So the obviously will show series of data showing secretly thing can inhibit is alliteration. This is one of the data showing you can use signal team purify Fusion protein, either human or mouse? Can you give it diesel proliferation and we also the Valley? Which is specific for signal 15 can inhibit tumor grows this is the image is growing in the body in the mouse and then you give anybody anything inhibit.

NOTE Confidence: 0.826930522918701

00:29:10.780 --> 00:29:23.470 So we did a site of profiling, which is this is still preliminary and data is quite interesting is the implying the MCC into the mice, which is why type or a significant markup.

NOTE Confidence: 0.845041275024414

00:29:24.030 --> 00:29:31.840 So wait. I'm versus Doc I'm not always show is red and you can see this we did. This is swimming, particularly interested in.

NOTE Confidence: 0.831370294094086

00:29:32.430 --> 00:29:51.160 What kind of change on my Roy sells right because my old cell is as I mentioned my loiselle is one of the major signals within powers and sells so on the left, you can see see VA in this dark. Amaze obviously tumor grow much slower then you can see the threat is not changing much here, XE D4.

NOTE Confidence: 0.833290278911591

00:29:51.670 --> 00:30:21.680 But CVA is clearly much higher in the Nakama is unclear. Sales also increase appears but my OS else. This is a very complicated. Phone number 7 Channel Channel #7 to 19. You can see this is a 13 different subsets of my liver cells based on the marker showing the right. This is all my OS else but it's different subset. Minor oysters and there's clearly this is some of some subset of my Roy sells unchanged.

NOTE Confidence: 0.862025916576386

00:30:21.810 --> 00:30:49.960 And some over change dramatically so this is the way still conducting further analysis to see as I mentioned Indiana early signal 15, only express in subset of Milo ourselves OK. This is the idea is not in order my or sell so that which is reasonable when we see this data, so the issue. Is there, which subset any unique feature can, we use that to predict the outcome so all these things is ongoing right now.

NOTE Confidence: 0.84774911403656

00:30:50.660 --> 00:31:06.860 So the 2 again this is a couple of the concept 3 different concept. We will talk about and use that we can developped the based on this guy by these principles, then we can actually.

NOTE Confidence: 0.867947101593018

00:31:07.790 --> 00:31:37.800 Come out the molecule like this so this as I mentioned this again. This is not the checkpoint OK check going pro. K means any inhibitors can be put on. I actually strongly against the ideas I think that's really what we're looking for because we have lots of experience only time from the so-called enhancement approaches. You can see when you push immune system to a certain level, then the price to pay is toxicities.

NOTE Confidence: 0.891962707042694

00:31:38.020 --> 00:31:46.990 So by this way by this more focused normalization approach you can actually avoid larger toxicities. You basically try to.

NOTE Confidence: 0.815069913864136

00:31:47.610 --> 00:32:02.130 You know to get fired on the micro environment rather than the whole body. This is a general ideas. So the now this entire SQL thing. Anybody is in criminal trial or their Phase 1, started last October.

NOTE Confidence: 0.870459735393524

00:32:02.650 --> 00:32:19.110 And the Phase 1, two together and the in collaboration with this cure companies and the illegible illegible patients 2 type of patience. One is patient have this all is patient. Every advanced solid tumors.

NOTE Confidence: 0.835513174533844

00:32:19.780 --> 00:32:45.160 Who either have a pedia one low OK typically pedia on low patients who sometime after screening they were not eligible for PD one treatment. So those are those are eligible for our treatment for our direct #2 is the patient is give anti PD or my PDR. One therapy and then they fail the therapy so you can see this type of the.

NOTE Confidence: 0.904382288455963

00:32:45.670 --> 00:32:49.420 The trial is not really competing with current the.

NOTE Confidence: 0.821892738342285

00:32:50.300 --> 00:33:09.290 Ongoing therapy or trials and biomarker. This this is above a study we take very seriously. We are going to do richer spectrum. We are doing each of introspective and perspective biomarker study try to identify the particular sub celebration as I mentioned the type strip Asian is.

NOTE Confidence: 0.804455041885376

00:33:10.090 --> 00:33:40.340 From that, we can start wings and the hospital in the country, the year. Leslie's Leaside demeans. The sample or close to us for analysis, so at least 1 result will be released. This is a place. One is basically is that the because from October. So the because this account for interest issues social with this and this skill center fountain this cool.

NOTE Confidence: 0.867616176605225

00:33:40.440 --> 00:34:10.810 So the I will not be able to talk, too much. But it's something I can tell you is number one in the freezer one result the truck is very safe, but we haven't seen much severe too much severe toxicities until unless drug use huge number so this is so it's very safe #2. We already see some responded so which is a single agent so I think this is the way very happy with that and hopefully.

NOTE Confidence: 0.846737682819366

00:34:10.810 --> 00:34:13.700 I think that's one reason will be released next month so.

NOTE Confidence: 0.839460492134094

00:34:15.550 --> 00:34:37.860 So the again this is a kind of summary what we target target full as I mentioned to you number type of two patient, which is now larger than or more than 50% anything from 51, PPL Center. Please by majority or other is not so then secretly team, which is target, very different subset of patients with a P 01.



NOTE Confidence: 0.855947017669678

00:34:38.630 --> 00:34:50.690 Lower or not or connected and this type of Asian have a piece of information every single team might benefit from that, we think is a simple team I also actually.

NOTE Confidence: 0.870728135108948

00:34:51.230 --> 00:35:13.980 Benefits summer patient in the PT1 PT 01 resistant patient and which could be could be interesting. These are our plastics. So then you can see here. Obviously type one and there before which is more than 50% of patients what we're going to do about. I can tell you where activity study that the idea is in our lab is in this type of patient.

NOTE Confidence: 0.845829844474792

00:35:15.630 --> 00:35:25.680 Is not as simply absence of the piece of infiltration? Is teaser actually cater single now not to come not to migrate.

NOTE Confidence: 0.891550362110138

00:35:26.220 --> 00:35:38.070 That, it is a reason is not simply because of the absence of of the Diesels. It's because our active mechanism operating in a tumor site and then.

NOTE Confidence: 0.852626442909241

00:35:38.780 --> 00:36:09.970 Cause these are not to come so this is from very basic science angle tool to approach this question. So this is very different from what right now is the mainstream idea, which is just can simply inject some of things, which can stimulate immune response directly into 2, there for example, taller receptors think or whatever into a tumor. Theoretically, which is most eventually right now already failing criminal trials and we think is if.

NOTE Confidence: 0.866625547409058

00:36:09.970 --> 00:36:41.520 Clearly active process or inhibitory mechanism in this type of tumor. Then the viewer not figure out their first then will not work. Obviously, try to force the email system. It's targeted work, so this is what we are working on so recap what I'm talking about. Here's an image therapy. I think is the basically is end of the beginning. The beginning means we care, some promising result. PD one PD. L1 we learn something we learn something very different.

NOTE Confidence: 0.852350294589996

00:36:41.520 --> 00:37:12.130 For all the traditional cancer immunotherapy, which is mostly based on idea or enhancement. So now I think we have different ideas is the obviously there's I'm not saying enhancement quesadilla service will be stopped handsome. I initially actually give lots of aliens, we know how immune system worked, how you can operate the issue is more like you have to watch the toxicities for normalization right now is the.

NOTE Confidence: 0.805221855640411

00:37:12.130 --> 00:37:42.200 Many targets still need to be discovered OK. This is what I think it's for the next many years. The efforts need to be put in here, so the obviously larger work as a major. Few people in the lab and the also there's a large team of the translation now and the clinical team is you see lawyer helps set there, they will rim crush operas pathologists and the.

NOTE Confidence: 0.839491367340088

00:37:42.200 --> 00:37:48.530 Caruso and their marriage know who is a clinical team, potentially involved in clinical trials. Thank you.